Table does not suggest the design of antisense oligonucleotides targeting all of the nucleotides encompassed by the claimed range." However, the Examiner's position is not supported by factual or legal evidence.

The specification describes antisense compounds that hybridize to nucleic acid molecules encoding ApoB and that inhibit ApoB expression. One such nucleic acid molecule encoding apoB is set forth in SEQ ID NO:3 and contains 14121 bases. The specification does not indicate that Applicants considered subranges falling within the broad range 1-14121 to be outside the scope of their invention. In fact, page 8 states that "the targeting process also includes determination of a site or sites within this gene for the antisense interaction to occur . . ." Table 1 (pages 91-92) sets forth exemplary compounds that hybridize to sites throughout nucleotide sequence set forth in SEQ ID NO:3 and inhibit expression of ApoB.

In determining whether numerical range limitations are supported by the description, one must consider the ranges that one skilled in the art would consider inherently supported by the original disclosure. MPEP 2163.06(III) citing *In re* Wertheim, 541 F.2d 257 (CCPA 1976). In *In re* Wertheim, the specification describes a range of 25%-60% and included specific examples of "36%" and "50%." Although claims having a limitation reading "at least 35%" were found not to be supported by the original disclosure because it included embodiments outside of the 25%-60% range, the court held that a limitation to "between 35% and 60%" did meet the description requirement. Here, Applicant has chosen to narrow the region of hybridization from 1-14121 of SEQ ID NO:3 to 1-114 and 151-14121 of SEQ ID NO:3. This range does not include embodiments outside of nucleotides 1-14121. Moreover, like in *In re* Wertheim, the exemplary molecules set forth in Table 1 would be viewed by one of skill in the art to inherently support the claimed range.

In making the rejection, the Examiner did nothing more than argue lack of literal support. This alone, however, is not enough to support a rejection under 35 U.S.C. § 112, first paragraph. *In re* Wertheim at 265. The Examiner has the burden of showing that the claimed invention is not described in the specification and to provide reasons why a description not in *ipsis verbis* is insufficient. By not providing any evidence or reasoning for the assertion that one skilled in the art would not view the claimed range as within Applicant's invention, the Examiner failed to establish a *prima facie* case of noncompliance

with the written description requirement. Thus, the rejection should be withdrawn.

The Examiner also asserted that some oligonucleotides within the range, e.g., SEQ ID NO:20 and SEQ ID NO: 24, did not display inhibitory effect. However, Applicant wishes to clarify the Examiner's misapprehension of the Table's data. The effect of SEQ ID NO:20 and SEQ ID NO: 24 are listed in Table 1 as "N.D.", which means "no data" as stated at page 89, line 31. Thus, Table 1 does not indicate that those oligonucleotides failed to display any inhibitory effect. Applicant also respectfully points out that present claim 1, for example, includes a functional limitation of inhibiting expression of a nucleic acid molecule encoding apolipoprotein B (ApoB). Thus, non-functional molecules that fall within the claimed range are not included within the claimed subject matter, and the existence of non-functional molecules does not seem to be relevant to the present rejection.

B. The rejection under 35 U.S.C. § 103(a)

Claims 1-2, 4-14, 20-23 stand rejected as assertedly being unpatentable over Chan *et al.*, (WO/01/12789) in view of Branch, Monia et al., and Agrawal *et al.* By purportedly describing inhibition of ApoB using a hammerhead ribozyme having portions that hybridize to nucleotides within the recited range of SEQ ID NO:3, the Examiner argues that Chan et al. provides motivation for designing nucleic acid based inhibitors for the purpose of inhibiting the expression of nucleic acid encoding ApoB mRNA. Moreover, the Examiner argues that it would have been obvious at the time of the invention to substitute ribozymes targeting ApoB mRNA with the non-catalytic antisense compounds of the present invention because they are both nucleic acid based and function to reduce the expression of a target mRNA. Applicant respectfully traverses the rejection.

Everything in Chan *et al.* is directed to ribozymes. As stated in the previous Response, ribozymes function by a completely different mechanism from the non-catalytic compounds of the present invention. The Examiner's assertion that the two very different classes of molecules are interchangeable remains unsupported.

Even if one assumes for the sake of argument that the ribozyme of Chan was inhibitory, such a teaching would be limited to other ribozymes, which carry their own catalytic mechanism. In contrast to ribozymes, non-catalytic compounds as claimed do not directly cleave target nucleic acids, but instead recruit and/or form the basis for complexes of

the target with proteinaceous RNA-cleaving enzymes. In fact, because ribozyme cleavage of nucleic acids may occur even when the ribozyme binds transiently to nucleotide sequences that are not the target sequence, the parameters for inhibition by ribozymes will be different from parameters for inhibition by non-catalytic compounds. Thus, even if a ribozyme inhibited expression of a nucleic acid, one of ordinary skill in the art would not find it obvious that a non-catalytic compound targeted to the same region would successfully inhibit expression of the target nucleic acid.

The secondary references are directed to general optimization guidelines for uses of antisense molecules. The secondary references do not disclose or suggest a recognition in the art of the interchangeability of ribozymes and non-catalytic antisense molecules. There is no suggestion in the cited art to excise the catalytic portion of the ribozyme of Chan *et al.* to produce a non-catalytic compound of the present claims. Moreover, such a modification would render the molecule incapable of functioning as a ribozyme. There can be no suggestion or motivation to make a proposed change in a prior art invention when such a change would render that invention unsatisfactory for its intended purpose. MPEP § 2143.01 citing In re Gordon, 733 F.2d 900 (Fed. Cir. 1984).

Furthermore, the cited art does not provide a reasonable expectation for success in inhibiting expression of a target nucleic acid by (1) removing the catalytic portion of a ribozyme or (2) targeting a non-catalytic compound to the target site of a ribozyme. Thus, the rejection fails to provide motivation for the modification of the ribozyme teachings of Chan *et al.* to arrive at the non-catalytic compounds of the present invention, and even if such motivation existed, the rejection fails to establish that one of skill in the art would have a reasonable expectation of inhibiting ApoB expression using the modified ribozyme of Chan et al.

Moreover, the Examiner improperly uses Applicant's own disclosure in setting forth the obviousness rejection. The rejection states on page 6 that it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the ribozyme of Chan et al. with the non-catalytic compounds of the present claims for the purpose of inhibiting expression of ApoB. But for Applicant's disclosure, however, one of skill in the art was not aware of the non-catalytic compounds of the present claims. Therefore, it could not have been obvious to those wanting to inhibit expression of ApoB mRNA to substitute the ribozyme of Chan et al. with the non-catalytic compounds of the present claims. Applicant

respectfully requests withdrawal of the rejection of claims 1-2, 4-14, and 20-23 under 35 U.S.C. § 103(a).

**Conclusion**

Applicant respectfully requests issuance of a timely Notice of Allowance. The Examiner is invited to contact the undersigned with any comments or suggestions that might expedite the issuance of the application.

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Respectfully submitted,

By _____

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